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The effects of stress and trauma on brain and memory: A view from developmental cognitive neuroscience

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Abstract

Many aspects of brain development depend on experience. Because the major macro-morphological events of brain development occur over the first 2–3 years of postnatal life, this time period can be considered both a period of opportunity as well as a period of vulnerability. In this paper we describe how experience with stress early in life can have a negative impact on certain aspects of brain development, and specifically, those neural circuits that underlie memory. We also describe the effects of traumatic events on the development of the neural basis of memory. In support of our argument, we review the literature on brain, stress, and memory in the context of development. Based on this review, we suggest that the developing brain is particularly vulnerable to the harmful physiological effects of stress, which in turn has the potential to lead to impairments in memory. Unfortunately, there are few empirical data that directly address this hypothesis. In this context we offer a number of suggestions for future research.

In this paper we examine the possible deleterious effects of stress on the developing brain, and at the behavioral level, on the development and formation of memory. The thesis that we will put forward is that stress acts on known neural circuits, a subset of which overlap with those that subserve memory. As a result, we will establish a potential neurological basis for stress-induced alterations in memory. In addition, because our research agenda is with the study of development we will cast this thesis in a developmental light.

Here we intend to demonstrate that the neural mechanisms at the cellular level that underlie functional plasticity, including long-term potentiation (LTP) and axonal regeneration, and that are adaptive in the normally developing child, will prove maladaptive to the child exposed to early, repetitive, and/or chronic stress. In other words, although plasticity in the developing brain represents a window of opportunity in normal circumstances, it also represents a period of vulnerability in adverse ones.

To provide a compelling argument in support of our thesis, we begin with a brief overview of memory and the neural bases of memory, and then proceed to discuss these topics in a developmental context. Here we conclude that the neural substrate required of explicit or declarative memory emerges during the first year of life, although much development awaits further elaboration of both limbic and cortical structures.

The next topic to which we turn is concerned with the effects of stress on the brain.

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Here we focus on both moderate levels of stress and acute and/or chronic levels, including trauma. Again, we begin with a review of the adult findings, and then turn to the child literature. Here we will make clear several known effects of stress on the brain. For example, stress can alter glucocorticoid receptors in regions of the hippocampus. In addition, some stressors can exert long-lasting, seemingly permanent effects on the brain. The dentate region of the hippocampal formation can experience permanent cell loss as a result of prolonged stress. Finally, the developing brain may be particularly vulnerable to stress. Exposing fetal monkeys to unpredictable loud sounds, for example, seemingly has permanent effects on postnatal neurobehavioral development.

Having established the link between brain and memory and between brain and stress, in the next section of our paper we attempt to integrate across these domains. Here we examine the neural bases of changes in memory that are stress-induced or perhaps more parsimoniously, stress-related. Because this is not the main area of activity of our laboratory, we will depend heavily on the work of other investigators. The developmental literature on this topic is not extensive, and a portion of our time will be spent on describing fruitful areas of future research. It will be these recommendations that will conclude our paper.

What Is Memory?

Although the jury is still deliberating, most cognitive psychologists agree that there are likely two major types of memory: explicit (or declarative) memory and implicit (or nondeclarative) memory. The former typically refers to memory that can be stated declaratively, that can be brought to mind as an image or proposition, that exists in some temporal time frame, and that, at least in the human adult, is memory of which we are consciously aware. In discussions of development, however, it may not be reasonable to impose the requirement of conscious awareness on the nonverbal organism, particularly the human infant (see Nelson, 1997, for discussion). Examples of explicit memory typi-

cally include the ability to recall events, objects, or places, or to recognize things associated with such events. Explicit memory can occur on a rapid time frame, in as little as one trial and under certain circumstances, may involve some aspect of "self." For example, the subject may see him/herself in some scene, such as what he/she was doing when John F. Kennedy was assassinated or when the space shuttle Challenger exploded.

Implicit memory, on the other hand, is typically thought to reflect a cluster of different subtypes of memory, although collectively, all are distinct from explicit memory. Indeed, perhaps a better way to frame this is that implicit memory as a whole represents a type of *nondeclarative* memory. Thus, all forms of implicit memory are assumed to be unconscious, to require multiple trials to acquire, and may not involve the self at all. One example of implicit memory is priming, which might involve presenting subjects with stimuli in a study phase that reappear briefly or in degraded form during a test phase. A subject's faster or more accurate identification of the test items relative to similar but unstudied items is taken as evidence of priming. A second form of implicit memory might be procedural learning. An example of a procedural learning task is the Serial Reaction Time (SRT) task, in which subjects are required to respond to a pattern of lights flashing across a screen. In such a case, the subject may show no overt, conscious awareness of learning the pattern; for example, when asked, "did you see a pattern," the subject might respond "what pattern?" Yet, despite the lack of awareness, the subject will nonetheless respond faster and faster, indicating that the pattern has been detected, albeit unconsciously. A partial list of other examples of implicit memory includes conditioning, skilled motor learning, and artificial grammar learning.

What is the Neurobiological Bases of Memory?

Although cognitive psychologists have conducted hundreds of clever and ingenious studies designed to distinguish these types of memory at the behavioral level (e.g., see Tul-

ving, 1985 for discussion), much of the evidence in support of this distinction has come from cognitive neuroscience. Here the question has been whether there are different neural systems that subserve these different types of memory. Based on several decades of research, it now appears that explicit memory depends disproportionately on structures that lie in the medial temporal lobe (e.g., hippocampus, rhinal cortex, parahippocampal gyrus), whereas the structures that subserve implicit memory vary depending on the subtype of memory being discussed. For example, visual perceptual priming likely depends on areas of the visual cortex, whereas auditory word priming might depend on the auditory cortex. Similarly, conditioning may depend on the cerebellum and certain brain stem nuclei. Procedural learning, such as portrayed in the SRT task, may depend on the basal ganglia (for an excellent overview of these systems, see Schacter & Tulving, 1994).

The human evidence in support of the neural dissociation of memory types typically comes from two sources. The first and most common is to study individuals who have suffered discrete lesions of the brain and examine the effects of performance on different memory tasks. A second is to perform neuroimaging studies of both brain damaged and neurologically intact individuals engaged in memory testing. A good historic example of the former, of course, can be found in patient H.M., who underwent surgical resection of both temporal lobes. Following the surgery, performed in 1953, H.M. was found to suffer acute anterograde amnesia; that is, he could form no new memories, although many types of implicit memory were intact (for an excellent lay history of this case, see Hilts, 1995). A more recent and even more startling example of the effects of brain damage on memory can be found in a study reported by Zola-Morgan, Squire, and Amaral (1986). These authors conducted lengthy and extensive testing on a patient referred to as R.B. At age 52 years, R.B. underwent coronary artery bypass surgery, with the unfortunate side effect being that he experienced an arterial tear that resulted in an acute ischemic episode. This interruption in the blood supply to his brain had

the effect of leaving him with severe anterograde amnesia. R.B. was of normal intelligence and performed normally in cognitive tasks except those involving explicit memory, on which he was severely impaired. After 5 years of study, R.B. died, leaving his brain to be examined by the investigators (see Schacter, 1996 for a summary of this case). Based on previous work by this group (for contemporaneous and subsequent reviews, see Squire, 1986, 1987, 1992, 1994), as well as work with monkeys in which selective lesions were performed (e.g., Bachevalier & Mishkin, 1984; Malamut, Saunders, & Mishkin, 1984; Mishkin, 1982; Zola-Morgan, Squire, Rempel, Clower, & Amaral, 1992), the authors predicted that R.B. would show evidence of damage to the hippocampus and surrounding cortex. Autopsy results were not only consistent with this, but even more impressive was the specific finding that hippocampal region CA1, one of several hippocampal regions containing pyramidal cells, was bilaterally destroyed by the ischemic infarct. It was thought that this selective damage was due to the vulnerability of this region of the hippocampus to metabolic disturbances, such as interruptions in blood supply (for discussion, see Squire & Zola-Morgan, 1991).

In neuroimaging studies, a standard approach to the study of function-structure relations in the context of memory is to have subjects perform some memory task while being examined using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). PET studies typically involve the injection of a radioactive substance, most often oxygen. The part of the brain most involved in performing the task will require more oxygen. As the radioactive oxygen diminishes, positrons are emitted, and a positron detector will essentially compute the point of origin of these particles; that is, will localize in the brain where they came from. In so doing, one is able to localize whatever function was being tapped by the task. In contrast, fMRI capitalizes on the fact that under strong magnetic fields, normally nonmagnetic materials will become magnetic (the principle of paramagnetism). Oxygen is one such material. Thus, as with PET the part of the brain most

involved in performing some task will place the greatest demands on oxygen. Over the course of seconds, this oxygen will gradually become deoxygenated, and it is these deoxygenated byproducts that can be observed under strong magnetic fields. This becomes manifest by superimposing this functional activity (i.e., deoxygenated blood) on to each subject's structural magnetic resonance image.

Using PET, Squire et al. (1992) have reported that regions of the right posterior cortex are activated during visual word priming and the right hippocampus to a greater degree than the left is activated during recall memory for words. Similarly, Ungerleider and colleagues have reported activation of the hippocampus and surrounding region during a variety of tests of explicit memory, using both PET and fMRI (for review, see Ungerleider, 1995). Collectively, then, the neuroimaging work correlates with the lesion work in confirming the view that there exists some degree of isomorphism between different types of memory and their underlying neural substrate.

Overall, a survey of the adult human and monkey literatures converge to suggest that explicit and implicit memory are dissociable at the behavioral level and, as well, are subserved by different neural systems. In the case of explicit memory, the hippocampus and surrounding structures (e.g., rhinal cortex) and the cortical structures communicating with these limbic structures play a primary role. In the case of implicit memory, the specific circuitry involved varies depending on the type of implicit memory (see previous discussion). Importantly, unless the subject begins to make explicit the task requirements, all forms of implicit memory are thought *not* to depend on the structures that subserve explicit memory. It is these observations that support the thesis that implicit and explicit memory represent different memory systems. In this next section we discuss these observations in the context of development.

The development of memory systems and their neurobiological bases

Unfortunately the study of the neurobiological bases of human memory development has re-

ceived very little study, with the exception of a handful of investigators interested in developmental cognitive neuroscience (see, in particular, empirical articles and reviews by Diamond, 1990, 1992, 1995; Diamond & Doar, 1989; Janowsky, 1993; Johnson, 1997; Nelson, 1994, 1995, 1996, 1997; and work by Bachevalier and colleagues on the developing monkey; for example, Bachevalier, 1992; Bachevalier, Brickson, & Hagger, 1993; Webster, Bachevalier, & Ungerleider, 1995). For the following reasons, this is not surprising. First, historically there has been a schism between the study of behavior and the study of the brain, with relatively little cross-fertilization between disciplines. Although this has changed dramatically over the past decade, especially in the field of adult cognitive neuroscience, change has been slower in the developmental sciences. Second, we know less about human brain development than we do about such development in nonhuman primates and nonprimates (particularly invertebrates), and as a result, our models of brain-behavior relations are underdetermined. Finally, and perhaps most importantly, the methods for studying the relation between brain development and memory development are far more limited when it comes to studying infants and young children than studying older children and adults. For example, although PET studies have been done routinely in children who present medical cause (e.g., ascertainment of a seizure focus, identification of dominant hemisphere for language, or effects of tumor on cognitive functions; see Chugani, 1994; Chugani & Phelps, 1986; Chugani, Phelps, and Mazziotta, 1987; Muller et al., 1997; Muller, Chugani, Muzik, & Mangner, in press), PET cannot readily be performed with normally developing children due to exposure to ionizing radiation. Similarly, fMRI has proved to be a powerful procedure for studying functional neuroanatomy in children older than the age of 5–6 years (see Casey et al., 1995; Nelson et al., 1998). However, such studies are difficult to perform with children below this age, primarily because of motion artifacts. Finally, in addition to the methodological limitations just described, it is also the case that the kinds of discrete brain injur-

Table 1. *Neural structures thought to underlie different memory tasks used in infancy and early childhood and maturational time table (in postnatal months/years) for emergence*

Tasks	Structures	Maturational Time Frame
Implicit memory		
Visual expectancies	Striatum	3–? months
Conditioning for		
Acquisition	Cerebellum/brain stem	3–? months
Retention	Hippocampus	1–12? months
Visual perceptual priming	Visual cortex + ?	6–? months
Serial reaction time	Caudate + ?	?–3/4 years
Preexplicit memory		
Visual paired comparison (no delay)	Hippocampus	0–3 months
Habituation (no delay)	Hippocampus? Rhinal cortex?	0–2 months
Explicit memory		
Visual paired comparison/habituation requiring categorization and/or delay	Hippocampus Rhinal cortex?	7+ months
Delayed nonmatch to sample (delay)	Hippocampus/rhinal cortex cortical area TE	12–?
Elicited imitation (delay)	Hippocampus + ?	9–12 months
Cross-modal recognition memory	Hippocampus/amygdala	6–12 months

ies that often afflict adults and that lend themselves to neuropsychological analyses of memory occur infrequently in children. For example, ischemic injuries that can selectively damage the medial temporal lobe, such as strokes and cardiac arrest, rarely occur in children. For all these reasons, then, it is not entirely surprising that there are relatively few cognitive neuroscience studies of memory development.

Recently one of us (Nelson, 1995, 1997) has proposed a model of memory development that has its basis in the neurosciences, and that has implications for understanding how early experiences (including stress) affect different memory systems. Drawing on research with nonhuman primates, neuropsychological and neuroimaging studies of adult humans, and the electrophysiological and behavioral development literatures on memory, Nelson has proposed that implicit and explicit memory can, in fact, be dissociated early in life (see Table 1). For example, studies of visual expectancy learning, in which infants' eye movements are observed to "ask" whether they observe a pattern in a series of moving lights, likely depends on the basal ganglia,

which is responsible for the acquisition of learned, voluntary motor movements (see Haith, Wentworth, & Canfield, 1993 for review). Similarly, studies of conditioning, such as leg-kick conditioning likely depend on the cerebellum for motor coordination as well as learning and associated brain stem circuitry, and possibly the hippocampus for recognition of novelty (see Rovee-Collier, 1997 for review). Priming has also been observed as early as 6 months of age (Webb & Nelson, 1998), suggesting yet another form of implicit memory that makes its appearance early in life. In contrast, studies employing the delayed non-match to sample (DNMS) procedure, in which the subject is presented with a sample stimulus and then, following some delay, is asked to distinguish the novel from familiar stimuli by retrieving the novel one, likely reflects a form of explicit memory. In addition, studies of cross-modal recognition memory and elicited imitation (see Bauer, Kroupina, Schwade, Dropik, & Wewerka, 1998) also likely measure forms of explicit memory. Importantly, Nelson proposed that the more mature forms of explicit memory, which depend on both the hippocampus and

surrounding structures, most importantly, the rhinal cortex and association cortices (e.g., area TE), likely do not develop until close to 1 year of age, and undergo considerable refinement over the next several years. One example would be the ability to verbally recall information; another would be the ability to remember information for long periods of time (e.g., months). Until cortical structures and the connections between the hippocampal circuitry and the cortical structures mature (which may not be until after 2–4 years of age), infants may not be capable of recalling events, simply because such events may not have been recorded into any permanent store.

Finally, there are forms of memory that Nelson referred to as pre-explicit memory, that depend principally on the hippocampus but not related structures. An example of pre-explicit memory might be simple novelty preferences observed in even very young (e.g., 2 month old) infants. Nelson proposed that pre-explicit memory undergoes a transformation as the child approaches 1 year to become the adult explicit memory system. It must be noted, however, that the system does not begin to reach adult-levels of maturity until the end of the preschool period (see Luciana & Nelson, 1998). Although Nelson did not do so at the time, it seems reasonable to speculate that what makes possible the changes in explicit memory through the preschool period is the development of various prefrontal functions that can come to the assistance of the medial temporal lobe (explicit) memory system. For example, it is generally not until the preschool period that children begin to routinely employ strategies to help them remember things; the use of strategies, of course, is a quintessential prefrontal function. In addition, being able to multitask (e.g., develop set and shift set while simultaneously encoding new material) is also a prefrontal function, one that again should facilitate an improvement in memory. Finally, an important component of memory development is the awareness that things can be forgotten, a form of metamemory that leads to understanding of the need to employ strategies. It seems reasonable to speculate that this oversight function of the brain also represents a func-

tion of the prefrontal cortex. Overall, then, although the neural machinery required of explicit memory matures rapidly between the child's first and fourth birthdays, it is likely the development of the prefrontal cortex, which also occurs around this time, that facilitates more sophisticated uses and forms of memory, including less forgetting and greater long-term storage.

Based on this model, it seems reasonable to offer the following proposals. First and most important, because an adult-like explicit memory system does not begin to emerge until close to 1 year of age and because the cortical systems that are involved in long-term memory storage and retrieval do not mature until after 2 years of age, the ability to *consciously* recall the events of our lives that occurred before the age of 2 or so years may prove difficult. This is particularly true as time passes, such as a 10-year-old recalling what happened 8 years previously. In contrast, as Bauer and colleagues (1998) demonstrate 2-year-olds may be able to "recall" highly specified events that occurred 6 months earlier, although the extent to which this is autobiographical memory in the conventional sense remains to be determined. It may be more parsimonious to suggest that recall observed before 2 years of age is explicit, but not necessarily episodic (autobiographical). For example, infants may recall the information that occurred in a previously encountered event, but may not recall the event in which they acquired this knowledge. This hypothesis is consistent with available neurobiological data on semantic and episodic memory. Episodic memory is more dependent on prefrontal structures that develop relatively late, while semantic memory is less dependent on these structures (Markowitsch et al., 1993).

This is not the forum for debating whether the sort of recall seen before 2 years of age differs from that seen later in development. Rather, it is simply our contention that we have seen no empirical evidence to support the claim that we are able to recall the episodes of our lives below the age of 2–3 years. Moreover, the bulk of the neuroscience evidence argues for our assertion that the development of the neural circuitry involved in

long-term memory develop slowly over the infancy and preschool period. The relevant structures that are thought to develop during this interval include the circuits that pass along information from the medial temporal lobe, where initial encoding and consolidation is performed, and the cortex, where memory is stored. It is neural maturation, then, that likely accounts for the gradual "recovery" from infantile amnesia.

Second, because the structures that underlie some forms of implicit memory may emerge before those that subserve explicit memory, there is the possibility that some early memories are in fact laid down in some permanent storage, although the child will not have conscious access to these memories. Here, then, we might expect such memories to express themselves in overt behavior (e.g., motor activity), or perhaps through covert physiological activity (e.g., skin conductance, event-related potentials), but not through any verbal means. It may well be this system that is responsible for how experiences in the first few years of life exert the powerful effects they do on later development, despite the fact that we cannot overtly recall these experiences. One such example may be priming, whereby an exposure to a stimulus at one point in time increases the probability of "recognizing" (albeit covertly) that stimulus at a later point in time. A hypothetical example of priming in a real-life context might be the strong emotional reaction a 2-year-old might have to a caretaker who physically abused the child 1 year earlier and whom the child has not seen since the abuse occurred.

Third, because the neural structures that subserve explicit memory undergo tremendous development over the first few years of life (particularly cortical structures), there should be a great deal of plasticity to this system. This plasticity, in turn, can be viewed as both a period of opportunity—that is, it may prove adaptive for the organism, such as learning—or a period of vulnerability—that is, it may prove maladaptive for the organism, as in disturbances in memory.

In the remainder of this paper we bring to bear the evidence that we believe supports our assertions, or lacking such evidence, offer

suggestions for the kinds of studies that need to be done to test our hypotheses.

Neural Plasticity and Memory

Later in this paper, we argue that the effects of stress on the developing brain represent an adverse form of neural plasticity. Before doing so, however, it would be useful to first demonstrate how neural plasticity might work to the advantage of the organism. To do so we first provide a model of neural plasticity, and then turn to some specific examples of plasticity from the monkey literature, and then move to the human.

Experience-expectant and experience-dependent plasticity

Learning and memory require nervous system modification, most likely by way of synapses formation. Greenough and colleagues (for review, see Black, Jones, Nelson, & Greenough, 1998; Greenough & Black, 1992) have proposed two mechanisms whereby synapses are formed, and thus the nervous system can be modified by experience. The first is referred to as *experience-expectant* synaptogenesis and is a processes by which synapses form after some minimal experience has been obtained. An oft-cited example is the development of binocular depth perception, in which normal visual input is necessary for ocular dominance to develop (Crair, Gillespie, & Stryker, 1998). If the two eyes are not properly aligned, thereby preventing them from converging effectively on a distant target, then such columns will fail to develop normally, and stereo vision will be compromised. If this condition is not corrected by the time the number of synapses begins to reach adult values (generally by the end of the preschool period), the child will not develop normal stereoscopic vision.

In contrast, *experience-dependent* synaptogenesis is a process that optimizes the individual's adaptation to unique features of the environment. A good example might be the information acquired by specific learning. The fundamental difference between experience-expectant and experience-dependent de-

velopment is that the former applies (presumably) to all members of a species, whereas the latter applies differentially to individual members.

In general, Greenough (e.g., Greenough & Black, 1992) has proposed that the structural substrate of "expectation" is the unpatterned, temporary overproduction of synapses that exist within a relatively wide area during a sensitive period. This sensitive period varies depending upon the system. For example, experience must be acquired during the first years of life for normal development of the visual system. Subsequent to the sensitive period, synapses that have not formed connections at all, or that have formed connections that are abnormal are retracted. The expected experience produces patterns of neural activity, targeting those synapses that will be selected for preservation. The model assumes that synaptic contacts are initially transient and require some type of confirmation (by way of experience) for their continued survival. If such confirmation is not obtained, synapses will be retracted according to a developmental schedule or as a result of competition from synapses that are clearly established. Support for this model comes from the observation that in both humans (e.g., Huttenlocher, 1994) and monkeys (e.g., Rakic et al., 1986), synapses are massively overproduced early in life, followed later by a pruning back of unused connections. Presumably the purpose of overproducing synapses is to prepare the nervous system for a broad range of possible experiences by overproducing connections on a widespread basis so that experience-related neural activity can select a functionally appropriate subset for further refinement.

As should be obvious, both experience-expectant and experience-dependent learning represent windows of opportunity and of vulnerability. Thus, if an experience occurs at the right time in development, the organism can take advantage of that experience and profit accordingly (e.g., learning). Similarly, if the *wrong* experience occurs (e.g., abuse or trauma) at the *wrong* time (i.e., when synapses are waiting for confirmation), then the result can be catastrophic; for example, mem-

ory and emotional impairments due to damage to the hippocampus and HPA axis.

In the section that follows we provide examples of plasticity in the context of memory. Our first example concerns the developing monkey, after which we turn to the human.

Neural plasticity of memory circuits

Webster, Ungerleider, and Bachevalier (1991b) have reported that in the intact (unlesioned) monkey, a transient projection is observed from inferior cortical area TE to the lateral basal nucleus of the amygdala. Interestingly, this projection is retracted later in development and is not present in the adult. However, when area TE, which is adjacent to TEO, is removed during the neonatal period (see Webster et al., 1991a), this normally transient projection *is* seen in the adult. In addition, transient projections from area TEO to the dorsal part of the lateral nucleus of the amygdala, which disappear in the adult, tend to expand into the zone normally occupied by terminals from area TE when TE is lesioned in infancy. Webster et al. (1991a, 1991b) have speculated that the sparing in performance on the DNMS task that has been noted with early TE lesions may be due to the retention of these early transient projections. Similarly, the presence of these transient projections early in life in the intact animal, followed by their retraction, may underlie the account of memory development outlined earlier. That is, pre-explicit memory that is solely dependent on the medial temporal lobe precedes the development of explicit memory, as the latter also depends on cortical area TE.

This example from the developing monkey nicely complements a recent report on the human. Vargha-Khadem, Gadian, Watkins, Connelly, Van Paesschen, and Mishkin (1997) reported on three case studies in which damage to MTL structures occurred either at birth (in two cases) or at the age of 9 years. All three patients, tested as adults, were reported to suffer from significant anterograde amnesia since the time of their injury. Neuropsychological evaluations confirmed significant impairments in memory at the time of study

participation. All three subjects showed impairments in spatial ability, in that they frequently got lost; in temporal ability, in that none was well oriented in place and time; and in episodic ability, in that none could reliably remember phone conversations, television programs, and so forth. In all three cases, MRI revealed bilateral hippocampal pathology, which would, of course, be consistent with their memory impairments. What was most remarkable about these individuals, however, is that all were attending or had attended regular schools; in addition, all performed in the average to low average range on a variety of tests that collectively reflected semantic memory. They had all learned to read, write, and spell (although one patient, born nearly 3 months prematurely and who at the age of 4 years suffered sustained seizures, had spelling that was not in the normal range) and their speech and language functions were normal, including normal acquisition of word meaning. The fact that all had reasonably intact semantic memory in the face of deep disturbances in episodic memory, and in the face of bilateral hippocampal damage, was a surprising outcome. That is, how could someone who cannot acquire new information (the hallmark of global anterograde amnesia) show sparing in semantic (i.e., fact-based) memory? The authors proposed that because the rhinal cortex was intact in these individuals, all retained the ability to form context-free semantic memories; however, because of hippocampal damage, none developed the ability to form context-rich episodic memories.

Because microscopic analyses cannot be performed on the brains of these individuals, it is difficult to determine whether a phenomenon like that reported by Webster et al. (1991b) might have also played a role in such sparing. Nevertheless, these data provide a compelling example of neural plasticity. Specifically, in the face of early, discrete brain damage, leading to permanent disability in a specific domain (episodic memory), compensation occurred permitting normal development in many domains. Unfortunately, as we shall see below, when discrete brain damage is not an issue but a psychological lesion such

as stress occurs early in life, the outcome may not be so favorable. After discussing the literature on stress, we will return to a discussion of differences between anatomic/physiologic lesions and psychological ones.

What is stress

Stress has been defined both behaviorally and physiologically. Behaviorally, stress has been thought of as any stimulus that threatens homeostasis (Diorio, Viau, & Meaney, 1993). That is, stress is something in the environment that might disrupt or change the normal functioning of an individual, including his or her very assumptions about the nature of the world and the self. Trauma involves stress that is more severe than and exceeds normal human resources for coping (Hubbard, Realmuto, Northwood, & Masten, 1995). Additionally, an important feature of traumatic events is the interpretation of them by the subject (Cicchetti & Toth, 1997). Unlike chronic stress, traumatic events can be single occurrences that have a profound impact on the individual and his or her development.

Physiologically, stress is defined by the activation of autonomic processes with which it is associated. The primary physiological stress response that has been characterized is the hypothalamic-pituitary-adrenal (HPA) axis. In this system, the hypothalamus releases corticosterone releasing factor (CRF) to the anterior pituitary. In response, the anterior pituitary synthesizes and releases adrenocorticotrophic hormone (ACTH). ACTH in the circulatory system reaches the adrenal cortex, where corticosterone or cortisol, depending on the system, is released (Stansbury & Gunnar, 1994). The HPA axis is regulated by a complex neural system. Under stress, cortisol production increases as a result of hypothalamic stimulation. After an initial increase in cortisol, inhibitory feedback systems in the brain, including the hippocampus and pituitary, reduce further release of CRF and ACTH (Sapolsky, Krey, & McEwen, 1986).

Stress, brain, and plasticity

A number of neural mechanisms are likely involved in the experience-dependent brain de-

velopment model. Of particular importance to the current discussion are two different ways in which stress may affect these mechanisms of development. Because the hippocampus contains one of the highest concentrations of glucocorticoid receptors in the brain, it is likely that high levels of glucocorticoids produced during stress may impact on the structure and function of the hippocampus. High levels of cortisol associated with prolonged severe stress have a number of impacts on the hippocampus. Direct application of high levels of corticosteroids *in vitro* can lead to atrophy in pyramidal neurons in the CA3 region of the hippocampus (Gould & McEwen, 1993; Sapolsky et al., 1986). The likely mechanism for this atrophy is the reduction in the apical dendritic tree of the CA3 pyramidal neurons as a result of interactions between glucocorticoids, excitatory amino acids, and glutamatergic receptors (McEwen, 1994). Likewise, in adult rats that are prevented from moving freely, a highly stressful event for a rat, atrophy in the apical dendrites of CA3 pyramidal neurons is also observed. Pyramidal neurons in the hippocampus play an important role in relaying information to other portions of the cortex. The importance of the hippocampus in consolidating and transporting memories into long term storage likely makes these cells critically important for normal memory function. Thus, factors that affect pyramidal cell survival, such as stress, may also affect memory. Loss of pyramidal cells in the hippocampus may contribute to stress-induced psychological lesions of the type we have hypothesized.

In addition, adrenal steroids also appear to contribute to increased levels of cell death and replacement in the dentate gyrus. Through its influences on cell birth and death in the hippocampus, stress may contribute to the equivalent of a psychological lesion similar to acquired structural lesions that have been observed in patients (Vargha-Khadem et al., 1997) or surgical lesions such as have been used in animal memory research (Bachevalier, 1990, 1992). In fact, such "lesions" have been seen in survivors of prolonged trauma who suffer posttraumatic stress disorder (PTSD), a topic that we discuss below.

Trauma

PTSD is characterized by persistent reexperiencing of a traumatic event, numbing and avoidant symptoms, and hyperarousal, and, specific to children and adolescents, repetitive play and a sense of foreshortened future (O'Dougherty Wright, Masten, Northwood, & Hubbard, 1997). Although there is relatively little available information on the effects of trauma on brain development and memory, there is reason to believe that trauma would adversely affect both. Unfortunately, it is virtually impossible to examine the effects of trauma in a prospective manner. Retrospective studies of the developmental neurobiology of trauma are limited in methodology because some standard methods in cognitive neuroscience are difficult if not impossible to use with children (as discussed earlier in this article). Further, even studies using methods that are applicable with children cannot be done until some time after the trauma occurs. Retrospective studies of brain and trauma have shown abnormalities in hormone regulation (Pynoos, Steinberg, Ornitz, & Goenjian, 1997), modulation of the startle response (Pynoos et al., 1997), increased hemispheric asymmetry in EEG (Teicher, et al., 1997) and increases in the slope of the P2-N2 deflection of the event-related potential (McPherson, Newton, Ackerman, Oglesby, & Dykman, 1997). Particularly important to our discussion of stress, trauma, and memory are the findings on hormone regulation. Stress hormones, as we will show, affect a number of systems and structures thought to be involved in explicit memory, such as the hippocampus. Further, hormones may also contribute to changes in the implicit memory system through interactions with the amygdala (Rooszendaal, Quirarte, & McGaugh, 1997). In addition to these physiological changes, neuroanatomical differences have also been observed, especially in the medial temporal lobe (Stien, Hanna, Koverola, Torchia, & McClarty, 1997). Magnetic Resonance images of the hippocampus of war veterans (Bremner, et al., 1995a) and childhood abuse survivors (Bremner, et al., 1997, Stein, Koverola, Hanna, Torchia, & McClarty, 1997) show reduced left hippocampal volume rela-

tive to nontraumatized controls. The lateralized nature of this reduction in hippocampal volume may be important in relation to memory deficits in patients with PTSD. As described below, there are specific memory impairments in adults with PTSD that may preferentially affect one hemisphere over the other. Unfortunately, in the absence of prospective studies, it is impossible to determine whether these effects are caused by trauma, or whether differences in neuroanatomy and/or physiology evidence an increased vulnerability to traumatic events.

Although the effect of the cognitive developmental status of the child has been proposed to contribute to the effect of trauma on the child (O'Dougherty et al., 1997), little is known about the effect of trauma on the cognitive development of the child. There is a great deal of debate about whether children can and do forget traumatic abuse and recover memories after a long period of time (Loftus, Garry, & Feldman, 1994; Williams, 1994a, 1994b). For example, there have been reports of dissociation, forgetting, and later memory retrieval in individuals who suffered documented abuse in childhood (see Duggal & Sroufe, 1998, for discussion). However, because of the necessarily retrospective nature of reports of forgetting and remembering in cases of abuse, and the reliance on self-report, it is nearly impossible to substantiate these claims. Interestingly, in addition to memory impairment in the face of trauma, there are also examples of heightened memory function. Patients with PTSD may suffer intrusive and persistent memories of their trauma, and may show other symptoms that may be associated with heightened *implicit* memory for the event (Bremner, Krystal, Southwick, & Charney, 1995). The neural mechanisms for this increase in implicit memory are poorly understood, and we will speculate on them later in the paper, but they may be associated with hormonal effects on the amygdala, which is important in, among other things, conditioned responses to highly affective stimuli (Roozendaal, Quirarte, & McGaugh, 1997). The dichotomous nature of memory symptoms in PTSD suggests that the deleterious effects of PTSD on memory vary dramatically

depending upon the memory system in question.

Effects of stress on memory

The effects of stress and trauma on the hippocampus and on brain development described above suggest at least two hypotheses about the effect of stress on memory. Performance on tests of hippocampal-dependent memory should be impacted by exposure to high levels of stress because of the effect of stress hormones on cell birth and death in the hippocampus. Work with animal models supports this hypothesis. Handling rats and placing them in novel environments reduces their level of performance in hippocampal-dependent maze learning tasks, but not in non-hippocampal dependent habit learning tasks (Diamond, Fleshner, Ingersoll, & Rose, 1996). However, this effect is transient, and dissipated when the rats became acclimated to the new environment so that it was no longer stressful. Stress has also been shown to facilitate some forms of learning that depend in part on the hippocampus, such as some forms of classical conditioning (Shors, Weiss, & Thompson, 1992). However, there are important differences between the types of hippocampal memory that are facilitated and impaired by stress. Although both forms of learning involve the hippocampus, the structures involved in each beyond the hippocampus differ dramatically. Classical conditioning involves the cerebellum and assorted brainstem nuclei, whereas declarative memory involves a complex circuit including the medial temporal lobe and cortical structures. More importantly, the stressor used by Shors et al. (inescapable shock) was very similar to the unconditioned stimulus used in the classical conditioning paradigm (preorbital shock paired with noise). It is not clear what the exact relation between the nature of the stressor and the nature of the memory trace is, or what is the effect of similarity between the two. However, given that intrusive, persistent, and heightened memory is one of the hallmark symptoms of PTSD, it is not altogether surprising that shock stress produces increased responsiveness to conditioned shock. Thus, is

it most likely the degree of stress and its duration that determines whether and for how long it will impair memory.

The effect of stress on the developing memory system is far less well described. Early stress could lead to long term memory deficits if the stress occurred during a time when the hippocampus is not yet fully mature and is vulnerable. For example, the development of object permanence is delayed in monkeys who were prenatally exposed to stress hormones, such as when their mothers were placed in stressful situations (Schneider, 1992). Specifically, pregnant monkeys were placed in cages in a darkened room and exposed to unpredictable loud bursts of noise. The infants of the stressed monkeys were older than control monkeys when they became able to find a hidden object on 80% of trials presented over two consecutive days, pointing to delayed development in the stressed animals. However, prenatal stress has a number of effects on monkeys' behavior and physiology (Clarke, Wittwer, Abbott, & Schneider, 1994; Vallee, et al., 1997). For example, in prenatally stressed monkeys, hormonal responsiveness to future shock is increased over nonstressed monkeys. As a result, it is difficult to conclude that the memory deficits observed by Schneider were a result of damage to the neurobiological memory system, or were a result of other behavioral consequences of prenatal stress exposure (such as increased release of acetylcholine in the hippocampus; see Day, Koehl, Deroche, Le Moal, & Maccari, 1998). In addition, Vallee and colleagues (1997) failed to find memory impairment in prenatally stressed adult rats. Nevertheless, it is clear from the results of work with prenatally stressed monkeys that there is an effect of early stress, either direct or indirect, on memory performance.

There is very little research that addresses the issues of memory, brain, and stress in humans directly (perhaps with the exception of Cushings Disease, which is not relevant to the present discussion). It is known that adults who suffer PTSD as a result of childhood abuse have been shown to have deficits in verbal, but not in visual short-term memory (Bremner, et al., 1995c). It is unclear why vi-

sual memory was unimpaired in this group of abuse survivors, but the findings are consistent with previous work by the same group in patients who suffered PTSD as a result of trauma in adulthood (Bremner, et al., 1993). One possible explanation is that because left hippocampal volume is reduced in PTSD patients (Bremner, et al., 1995a, 1997), and the left hemisphere is thought to be more involved than the right hemisphere in language processing, abilities that rely on linguistic competencies, such as verbally memory, are especially vulnerable to the effects of stress.

If the reports of alterations in brain development hold, it is important to identify the mechanisms involved in the process. We propose that developmental plasticity, although advantageous in the normally developing child, can adversely impact the child developing under adverse conditions. Because the developing brain is plastic and easily molded by the environment, it is especially vulnerable to the effects of stress and trauma. Thus, the mechanisms that are involved in aberrant brain development may be the same mechanisms that are involved in normative plasticity in the developing nervous system. One mechanism that may play a particularly important role in the development of memory system is plasticity at the synaptic level.

Stress appears to impact synaptic plasticity. In perhaps the most well-described form of synaptic plasticity in the hippocampus, LTP, a prolonged burst of high frequency activity leads to increased responsiveness of the synapse to later activation. The mechanisms involved in LTP include the activation of glutamate receptors and subsequent changes in both the pre- and postsynaptic neuron. LTP has been proposed as a model for memory formation because it requires repeated and synchronous activation of two neurons, meeting the requirements laid forth by Hebb (1949) for a cellular mechanism for memory (i.e., it involves high frequency stimulation of a presynaptic cell that ultimately leads to increased responsiveness of the postsynaptic cell). Further, because glutamate receptors and glucocorticoids likely are coinvolved in hippocampal cell death resulting from high levels of glucocorticoid exposure, there is pre-

sumably an interaction between glucocorticoid exposure and LTP. Indeed, very high and very low levels of corticosteroids leads to a reduction in LTP in the hippocampus (Filipini, et al., 1991, Dubrovsky et al., 1993, McEwen, 1994). Because LTP in the hippocampus has been hypothesized as a mechanism for memory formation, decreased LTP as a result of high levels of stress may lead to reduced ability to form memory traces.

In addition to its role in memory formation, LTP may have other roles in the normative development of the nervous system. In the developing visual system, for example, LTP appears necessary for normal development of the visual circuit (Katz & Shatz, 1996). Although there are no data on the role of neural activity in the development of the circuits involved in memory, given that other neural systems require this mechanism, and given that LTP is known to occur in the earliest developing structures in the circuit that controls explicit memory, it seems plausible that LTP could be involved in normative development of this system during the first year of life. Thus, disruptions to LTP as a result of high levels of stress-induced cortisol in the hippocampus could disrupt the basic formation of the explicit memory system.

Relatively little is known about the effects of stress on the development of the neural systems involved in memory. There is some evidence that glucocorticoid levels can affect cell proliferation in some parts of the central nervous system. Reduced levels of glucocorticoids following adrenalectomy leads to an increase in the number of proliferating cells (Yehuda et al., 1989). Together with the likely role of stress hormones in cell birth and death (Gould & McEwen, 1993), it would seem plausible that exposure to high levels of stress hormones in the period during which memory is developing (i.e., the first few years of life) would have a negative impact on the neural basis of memory.

Conclusions and Suggestions for Future Research

Experimental evidence from a number of animal models and clinical evidence from hu-

mans yield a complicated picture of the effects of stress on memory. It appears that parts of the brain that are critically involved in memory are uniquely impacted by stress. However, the effect of stress on memory performance appears to differ depending on the species studied, the timing, duration and severity of the stressors, and the age of the subjects when tested. Several questions must be addressed before the effect of stress on memory development can be clarified. First, we must describe the effects of stress and stress hormones during the period before which the hippocampal-dependent long-term memory system is in place. Lesion studies have shown that the anatomy of the medial temporal lobe memory system can be altered by early lesions to its components (Webster, Bachevalier, & Ungerleider, 1995). The effect of early experiences on those connections must also be described. We have recently shown that imaging techniques typically used with adults (e.g., fMRI) can be used to describe the functional neuroanatomy of working memory in children (Nelson et al., 1998). This methodology is particularly important given the earlier discussion of "psychological" lesions. Functional imaging studies can provide both functional and neuroanatomical information about the effect of stress and stress hormones on the development of the brain. These methods can be applied to children in a variety of clinical conditions. One such population might include children who are given repeated doses of exogenous glucocorticoids as treatment for asthma. Not surprisingly, it has been observed that such children suffer deficits in memory (Annett & Bender, 1994). A second example would include children suffering from chronic or acute psychological stressors, such as those repeatedly separated from their primary caretaker because of illness or abuse. A final example is very premature infants who are treated with steroids. Such infants typically receive steroids to facilitate lung development, and in so doing reduce the amount of time such infants receive ventilatory assistance and reduce the chances of the child from developing bronchopulmonary dysplasia (BPD). BPD is characterized by scarred lungs, which in turn predisposes the child to chronic airway

difficulties (e.g., a vulnerability to upper respiratory infections, etc.). Although infants have benefited enormously by being treated with steroids (for review, see Neal, 1997), the down side is that the child is at risk for two potential problems. The first, of course, is damage to the HPA system, and with it the attendant risk of suppressing the child's stress response. The second is the potential damage that could occur to the hippocampus and in turn, to the development of memory.

Because of the potential adverse effect of steroid hormones on the hippocampus, the development of children in the above examples must be examined, both for our understanding of memory development and for the potential impact of the therapy on the child. However, the neural correlates of these deficits must also be described. Finally, methods that are

appropriate for the study of the neural basis of memory development must be applied to the question of the effect of early stress on memory during the time that the neural substrate of memory is developing.

Overall, it is our contention that there is compelling evidence to support the thesis that the developing nervous system is potentially vulnerable to the deleterious, long-term effects of stress on memory. Given the availability of study populations (e.g., children who undergo chronic psychological stressors or children who are exposed to high levels of exogenous steroids), and methods for examining the relation between brain and memory (e.g., event-related potentials and fMRI, coupled with well defined psychological tasks), it was our hope in this paper to provide a conceptual framework that will facilitate such work.

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